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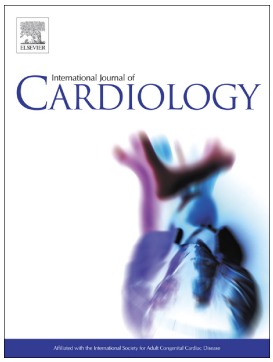

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Residual vegetation after treatment for left-sided infective endocarditis and subsequent risk of stroke and recurrence of endocarditis

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Abstract

Background: Little is known about the subsequent risk of stroke and recurrence of IE for patients surviving infective endocarditis (IE) with a residual vegetation at discharge.

Methods: Patients were consecutively included in the East Danish Endocarditis Registry from 2002-2012. We included patients undergoing medical treatment only during IE admission who were discharged alive. Size of residual vegetation was assessed by echocardiography at discharge and patients were categorized according to median length of residual vegetation. Using multivariable adjusted Cox Proportional hazard analysis, we assessed the associated risk of stroke and recurrence of IE between study groups.

Results: Among 915 IE patients, 305 were included after selection criteria were applied, 151 patients without residual vegetation, 73 patients with 1-5 mm residual vegetation, and 81 patients with >5 mm residual vegetation. We identified an increased associated risk of stroke for patients with 1-5 mm and >5 mm residual vegetation, HR=0.88 (95% CI: 0.26-2.94) and HR=2.95 (95% CI:1.18-7.34) compared with patients without residual vegetation. No difference was seen between groups for the associated risk of recurrence of IE, HR=1.39 (95% CI: 0.91-2.13) and HR=1.38 (95% CI: 0.91-2.10) for patients with a residual vegetation 1-5 mm and >5 mm compared with patients without residual vegetation.

Conclusions: Patients surviving IE with a residual vegetation >5 mm had an increased associated risk of stroke compared with patients without residual vegetation. These findings provide new perspectives on a patient group sparsely describe, suggesting a potential benefit of therapy among patients surviving IE with a residual vegetation >5 mm.

Introduction

The mortality and morbidity in patients with infective endocarditis (IE) remains high and few studies have addressed the prognosis of patients surviving IE.[1,2] Vegetation size at time of diagnosis has been associated with an increased risk of embolic events and increased risk of mortality.[3] Little data are available on patients surviving IE with a residual vegetation and the subsequent risk of stroke and recurrence of IE. It is estimated that 20-40% of patients with IE experience a stroke[4] and vegetation size has been found to be a risk factor for cerebrovascular lesions and death.[3,5,6] To prevent embolic events during the course of IE, vegetation size may be an indication for surgery in patients with IE.[7] In patients surviving IE with residual vegetation, data on the associated risk of stroke and recurrence of IE could help clarify if these patients potentially could benefit from additional therapy after discharge e.g. antithrombotic treatment. The incidence of ischemic stroke in patients surviving IE have been estimated at 17.4 / 1,000 person years, which is more than 1.5 times higher compared with matched controls from the background population.[8] These data underline the need to address this issue in more detail.

Recurrence of IE has been found to occur in 2.2% in a cohort from a referral center.[9] Recurrence of IE is a major concern since the prognosis of patients with recurrent IE is substantial worse compared with patients with first-time IE.[10] Still, few data underlines the American and European recommendations on short-term follow-up after IE.[7,11] In a scientific statement from the American Heart Association and in the current guidelines from the European Society of Cardiology (ESC) recommendations are regularly clinical and echocardiographic follow-up, particularly in the first year after discharge.[7,11] Data on patients with residual vegetation and the associated risk of subsequent stroke and recurrence of IE may help differentiate which patients should be followed more closely. The objective of this study was to investigate the associated risk of subsequent stroke and recurrence of IE in patients surviving IE by the size of residual vegetation.

Methods

Data sources and study population

The Danish health care system is universal and tax paid. Every Danish citizen is provided with a unique identifier making it possible to link clinical and administrative registries.[12] We used The East Danish Endocarditis Registry, which consecutively enrolled patients with IE from 2002-2012 from Gentofte Hospital and Rigshospitalet (referral centers). As previously described, the registry holds information on demographic, clinical and paraclinical findings at baseline, bacterial etiology, surgical intervention, and echocardiographic data at hospitalization and discharge.[13] Further, we used The National Patient Registry, which holds information on every hospitalization in Denmark since 1977. The registry is derived from codes based on the International Classification of diseases (ICD) from discharge forms. The ICD-8 was used until 1994 and the ICD-10 was used subsequently. To identify patients with systemic arterial hypertension, we used antihypertensive medication from The National Prescription Registry. These registries has been characterized in details previously.[14,15]

Echocardiography and size of vegetation

Echocardiograms performed up to seven days prior to the date of discharge was considered as the discharge echocardiogram. In the absence of data from a transesophageal echocardiogram (TEE), the transthoracic echocardiogram (TTE) was used. A residual vegetation was defined as an oscillating or non-oscillating intracardiac mass, as previously described.[16] The maximum length of the vegetation was used to evaluate the size of the vegetation. Data on left-sided valve regurgitation at IE discharge was available from the East Danish Endocarditis Registry. Severity of the regurgitation was assessed using a combination of qualitative, semi-quantitative, and

quantitative measures.[17] For patients with regurgitation of both the aortic and the mitral valve, the patient was categorized according to the most severe regurgitation.

Study population

The study population was derived from The East Danish Endocarditis Registry, including only patients with left-sided IE. We excluded 1) patients who died during IE-hospitalization, 2) patients who underwent surgery before discharge, 3) patients who did not have an echocardiogram performed at discharge, and 4) patients who had right-sided IE and pacemaker IE, see Figure 1 for the patient selection process. The study population was grouped in 1) patients without residual vegetation 2) patients with a residual vegetation below the median length of the vegetations (1-5 mm), and 3) patients with a residual vegetation above the median length of the vegetations (>5 mm).

Covariates, endpoint and follow-up

Patient characteristics at baseline were assessed at admission through medical records and patient interview. Atrial fibrillation before IE admission was assessed through the National Patient Registry with an in-hospital or out-patient diagnosis code in a period of up to ten years before IE admission. Systemic arterial hypertension was assessed as a confounding covariate, which was defined as antihypertensive through the National Prescription Registry with at least two filled prescriptions for antihypertensive medication within six months prior to IE admission, see Supplementary Table 1 for specific codes. The primary endpoint of our study was stroke, which was identified from the National Patient Registry. Only a primary in-hospital diagnosis with one of the following ICD-10 codes: I61-I64 was used. These codes have been validated with a positive predictive value between 74% and 97% in the National Patient Registry.[18] Secondary endpoints were 1) recurrence of IE and 2) all-cause mortality. Recurrence of IE was identified from the National Patient Registry using

in-hospital, primary or secondary diagnosis code (ICD-10 codes: I33, I38, I398). Only patients with a length of hospital stay ≥14 days were included unless the patient died within 14 days of the hospital stay. The IE-codes have been validated with a positive predictive value of 90%.[19,20] Date of death was identified from The Cause of Death Registry. Heart valve surgery was considered as competing event and the National Patient Registry was used to identify heart valve surgery during follow-up (procedure codes: KFK [mitral valve surgery] and KFM [aortic valve surgery]). We followed patients from the date of IE discharge until date of: stroke, recurrence of IE, death, heart valve surgery, end of the study period (31 December 2016), or a maximum of five years of follow-up, whichever came first.

Statistics

Baseline characteristics were presented by study group (residual and no residual vegetation). Categorical variables were presented in counts and percentages, while continuous variables were presented with a median and 25 and 75 percentiles. Plots of the cumulative incidence of stroke and recurrence of IE were plotted for the two study groups using the Aalen-Johansen estimator. In the analysis of stroke we accounted for valve surgery, recurrence of IE, and death as a competing event and for recurrence of IE, valve surgery and death was accounted for as a competing event. Gray's test was used to identify difference between curves. Kaplan-Meier plots were used to illustrate differences in mortality rate by the three groups. The log-rank test was used to identify difference between the Kaplan-Meier curves. Multivariable adjusted Cox proportional hazard analysis was used to identify the associated risk of stroke, recurrence of IE, and mortality in patients with 1-5 and >5 mm vegetation compared with no residual vegetation. The following covariates were included in the models investigating the associated risk of stroke and the risk of all-cause mortality: residual vegetation, chronic renal impairment, atrial fibrillation, diabetes mellitus, hypertension (defined from antihypertensive medication), prosthetic heart valve, sex and age. For the model investigating

the associated risk of recurrence of IE the following covariates were included: residual vegetation, chronic renal impairment, native heart valve disease, prosthetic heart valve, prior IE, causative microorganism, sex and age. Further, in an additional analysis, we examined the associated risk of IE relapse (within six months of follow-up) and the associated risk of recurrence of IE (beyond six months of follow-up). The proportional hazard was tested using Martingale's residuals and if violated follow-up time was split in time intervals. Linearity was tested for continuous variables. We tested if there was an interaction with significant valve regurgitation (moderate or severe) and residual vegetation on recurrence of IE. In a supplementary analysis, residual vegetation was included as a continuous variable in the regression model. In a sensitivity analysis, we excluded patients with a prosthetic heart valve at the time of IE-diagnosis to account for the increased risk of stroke and IE compared with patients with native valves. Results were presented with a hazard ratio (HR) and a 95% CI. A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using the SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, NC, USA) and RStudio.

Results

A total of 915 patients were screened from the East Danish Endocarditis Registry, including a total of 305 patients, 151 patients without a residual vegetation, 73 patients with a 1-5 mm residual vegetation, and 81 patients with a >5 mm residual vegetation, see Figure 1. The majority of patients were male with a similar median age between 68 and 70 years for all groups, Table 1. All patients had an echocardiography performed at IE discharge with over 95% of patients who had a TEE conducted at discharge. Patients without residual vegetation had more often a prosthetic heart valve and more often aortic valve IE compared with patients with 1-5 mm and >5 mm residual vegetation, Table 1. Patients with a residual vegetation 1-5 mm were more often on antihypertensive

medication compared with the two other groups, Table 1. Patients were followed for a median of 3.6 years (25 and 75 percentiles: 0.7-5.0 years).

Risk of stroke

The cumulative risk of stroke at five years of follow-up was 6.6% (n=10), 5.5% (n=4) and 12.3% (n=10) for patients without residual vegetation, 1-5 mm vegetation, and >5 mm residual vegetation, respectively, Figure 2 (p=0.21 for difference between curves). In multivariable adjusted analyses we found an increased associated risk of stroke for patients with >5 mm residual vegetation compared with patients without a residual vegetation, Figure 3. No difference was seen between patients with a residual vegetation of 1-5 mm compared with patients without a residual vegetation, Figure 3. Including residual vegetation as a continuous variable in the multivariable adjusted regression model, we found an increased associated risk of stroke per one mm increase in residual vegetation, HR=1.08 (95% CI: 1.00-1.17).

Recurrence of IE

The cumulative risk of recurrence of IE with up to five years of follow-up was 16.0%, 11.0%, and 18.5% in patients without residual vegetation, with 1-5 mm residual vegetation, and >5 mm residual vegetation, respectively, Supplemental Figure 1 (p-value=0.41 for difference between curves). In a multivariable adjusted analysis, we found no statistically significant difference in the associated risk of recurrence of IE for patients with a residual vegetation 1-5 mm and >5 mm, HR=0.66 (95% CI: 0.29-1.53) and HR=1.34 (95% CI: 0.69-2.64) compared with patients without residual vegetation. We identified a non-significant associated risk of recurrence of IE when including residual vegetation as a continuous variable in the multivariable adjusted regression model, HR=1.04 (95% CI: 0.97-1.11).

With up to six months of follow-up, we found a cumulative risk of 9.9% (95% CI: 5.8-15.3%),

8.2% (95% CI: 3.3-16.0%), and 9.9% (95% CI: 4.6-17.6%) for patients without residual, 1-5 mm residual vegetation, and >5 mm residual vegetation (p-value for difference in associated risk of IE relapse 0.49). Beyond six months of follow-up, we found a cumulative risk of IE of 7.5% (95% CI: 3.7-13.2%), 3.4% (95% CI: 0.6-10.5%), and 6.9% (95% CI: 2.2-15.4%) for patients without residual, 1-5 mm residual vegetation, and >5 mm residual vegetation (p-value for difference in associated risk of IE recurrence 0.59).

Mortality

The five-year all-cause mortality rate was 40.3%, 54.0% and 50.9% for patients without residual vegetation, 1-5 mm residual vegetation, and >5 mm residual vegetation, respectively, Supplemental Figure 2 (p=0.09 for difference between curves). In a multivariable adjusted analysis, we found no statistically significant difference in mortality for patients with a 1-5 mm residual vegetation and >5 mm residual vegetation, HR=1.39 (95% CI: 0.91-2.13) and HR=1.38 (95% CI: 0.91-2.10), respectively compared with patients without a residual vegetation.

Regurgitation and valve surgery during follow-up

We found that 40 patients (26.5%), 26 patients (35.6%), and 35 patients (43.2%) were discharged with a moderate or severe left-sided valve regurgitation among patients without residual vegetation, 1-5 mm, and >5 mm residual vegetation, respectively, see Supplementary Table 2 for details on valve pathology. During follow-up, 11 patients (7.3%), 4 patients (5.5%), and 14 patients (17.3%) underwent left-sided heart valve surgery in patients without residual vegetation, 1-5 mm, and >5 mm residual vegetation, see Supplementary Table 3. Significant valve regurgitation did not influence the effect of residual vegetation on the associated risk of recurrence of IE (p=0.61 for interaction).

Sensitivity analysis

In a sensitivity analysis, we excluded 114 patients with a prosthetic heart valve (47 patients with a mechanical heart valve and 67 patients with a bioprosthetic heart valve). We included 191 patients in the additional analysis; 82 patients (42.9%) without a residual vegetation, 51 patients (26.7%) with a 1-5 mm residual vegetation, and 58 patients (30.4%) with a >5 mm residual vegetation. In a multivariable adjusted analysis, we identified that patients with 1-5 mm was associated with a non-significant increased risk of stroke, HR=2.89 (95% CI: 0.24-34.86), and >5 mm residual vegetation were associated with a significant increased risk of stroke, HR=11.91 (95% CI: 1.35-104.79) compared with patients without a residual vegetation. For recurrence of IE the estimates were: HR=1.03 (95% CI: 0.32-3.33) and HR=1.42 (95% CI: 0.54-3.76) for patients with a 1-5 mm and >5 mm residual vegetation compared with no residual vegetation. For all-cause mortality the estimates were: HR=1.57 (95% CI: 0.89-2.76) and HR=1.29 (95% CI: 0.75-2.24) for patients with a 1-5 mm and >5 mm residual vegetation compared with no residual vegetation.

Discussion

We investigated patients surviving IE and the associated risk of stroke, recurrence of IE, and mortality in patients without residual vegetation, 1-5 mm, and >5 mm residual vegetation. Our study had three major findings, 1) patients with a residual vegetation >5 mm were associated with an increased risk of stroke compared with patients without a residual vegetation, 2) for every millimeter increase in residual vegetation, we identified a significant increased associated risk of stroke, 3) No difference was seen in the associated risk of recurrence of IE between groups.

Patients treated for IE, who are clinically stable, can be discharged although residual vegetation exist, however the subsequent risk of stroke and recurrence of IE has remained unknown.[16] Several studies have investigated length of vegetation, measured in the initial phase of IE, and the associated risk of embolism in these patients.[3,21–23] All studies identified an increased

associated risk of embolism for patients with a vegetation length of >10 mm[21,23], >15 mm,[3] or ≥30 mm[22] and cerebrovascular complications have been related to an increased mortality in IE patients.[5] Assessing vegetation length in the initial course of IE is a cornerstone in guidance of surgical therapy since vegetation length in the initial phase of IE is a risk factor of cerebrovascular events during the course of IE.[7] Up until now it has been unknown if a residual vegetation in patients surviving IE has increased the associated risk of subsequent stroke. Our results suggest an increased associated risk of stroke in patients with residual vegetation >5 mm compared with patients without residual vegetation. Platelet activation and thrombus generation around the vegetation may be an explanation to this finding and, speculatively, platelet inhibition may be beneficial in this patient group.

We observed no significant differences in the risk of recurrence of IE for patients with 1-5 mm and >5 mm residual vegetation compared with patients without residual vegetation. One may have hypothesized that a residual vegetation may be a source of increased blood turbulence increasing the risk of recurrence of IE and. Our results on recurrence of IE may be underpowered and these results should be interpreted with caution.

We identified a trend towards an increased mortality in the two patient groups with residual vegetation compared with patients without residual vegetation. A study by Thuny et al. identified an increased mortality for patients with a vegetation length >15 mm measured in the initial course of IE.[3] Differences between the results of Thuny et al. and our findings may be differences within the populations studied and the timing of echocardiographic assessment of the vegetation length. We only included patients undergoing medical treatment for IE and patients discharged with a vegetation >10 mm may have had an indication for surgery.[7] A high burden of comorbidities may be reflected in the clinical decision of not performing surgery in patients with a vegetation >10 mm, which could explain some of the difference seen in mortality rates between groups.

The ESC guidelines on IE states that patients treated for IE needs close clinical follow-up, especially in the first year after IE discharge.[7] Serial echocardiograms are suggested in the prevention of secondary heart failure and management of valve regurgitation follows ordinary guidelines on this subject.[7,17] However, specific guidance of how to manage patients with residual vegetation are not described. It has previously been shown that early surgery decrease the risk of a composite of embolic events and death in the acute phase of IE.[24] Our results provide new perspectives on these previous findings, suggesting a potential benefit of therapy among patients with a residual vegetation >5 mm. Cardiac surgery could potentially be conducted to remove the vegetation, however this approach may carry an even higher risk of stroke and adverse events in itself.

Limitations and strengths

Our study has some limitations. First, our study may be underpowered consequently leading to a type II error. Second, we are not able to identify if patients were discharged to hospice/palliative care or a nursery home. Third, more extensive echocardiography details would have added additional knowledge, such as the morphology of the residual vegetation. Fourth, data from brain imaging scans were not available from the registries. Such data could have helped describe the mechanism of stroke in detail. Fifth, laboratory values such as International Normalized Ratio (INR) subsequent to IE discharge was not available, which is important for patients with a mechanical prosthetic heart valve and the risk of stroke.

Although limitations of this study exist, we believe the study has strengths as well. This study was able to combine a clinical registry with nationwide administrative registries allowing for clinical details with long-term follow-up from well-validated hospital codes on stroke and IE. The novelty of this combination gives unique insight to patients surviving IE, which has been sparsely described previously.

Conclusion

Our results suggest that patients surviving IE with a residual vegetation >5 mm has an increased associated risk of stroke compared with patients without a residual vegetation. These findings provide new perspectives on a patient group sparsely describe, suggesting a potential benefit of therapy among patients surviving IE with a residual vegetation >5 mm.

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Figure legends

Figure 1. Patient selection process

Figure 1. The figure shows a flow chart of the patient selection.
IE: infective endocarditis.

Figure 2. Cumulative incidence of stroke

Figure 2. The figure shows the cumulative incidence of stroke for patients without residual vegetation, 1-5 mm residual vegetation, and >5 mm residual vegetation.

Figure 3. Associated risk of stroke

Figure 3. The figure shows the associated risk of stroke for patients with 1-5 mm residual vegetation and >5 mm residual vegetation compared with patients without residual vegetation in a crude and multivariable adjusted regression model. The multivariable adjusted analysis was adjusted for: prior IE, prosthetic heart valve, microbiologic etiology, sex, age, chronic renal impairment, native valve disease.

Table 1. Baseline characteristics

	No residual vegetation	1-5 mm residual vegetation	>5 mm residual vegetation	p-value
Demographics				
Number	151	73	81	
Male, n (%)	106 (70.2)	42 (57.5)	63 (77.8)	0.07
Age (years), median (IQR)	68.0 (56.0-78.0)	70.0 (64.0-77.0)	68.0 (60.0-78.0)	0.49
TEE at discharge, n (%)	144 (95.4)	70 (95.9)	78 (96.3)	0.94
Length of residual vegetation, median in mm (IQR)	-	4 (2-5)	8 (7-10)	
Comorbidity, medical history prior to IE, n (%)				
Pacemaker	12 (8.0)	7 (9.6)	8 (10.0)	0.85
Chronic renal impairment	19 (12.6)	12 (16.7)	13 (16.3)	0.63
Diabetes mellitus	18 (11.2)	17 (23.3)	12 (14.8	0.086
Cancer at admission	11 (7.4)	6 (8.2)	9 (11.1)	0.62
Neurologic disease	20 (13.3)	7 (9.6)	10 (12.4)	0.80
Atrial fibrillation	46 (30.5)	22 (30.1)	14 (17.3)	0.075
Antihypertensive medication*	60 (39.7)	48 (65.8)	34 (42.0)	0.001
Predisposing conditions, n (%)				
Native valve disease	21 (14.1)	13 (18.1)	16 (20.0)	0.66
Prosthetic valve	69 (46.0)	22 (31.0)	23 (29.1)	0.017
Previous IE	14 (9.5)	4 (5.6)	7 (8.8)	0.60
Intravenous drug abuse	5 (3.3)	-	-	0.27
Immunosuppressant therapy	15 (10.2)	11 (15.7)	6 (7.6)	0.27
Site of infection, n (%)				0.009
Aortic	81 (53.6)	27 (37.0)	32 (39.5)	
Mitral	57 (37.8)	28 (38.4)	33 (40.7)	
Aortic and mitral	13 (8.6)	18 (24.7)	16 (19.8)	
Microbiologic finding, n (%)				0.47
Hemolytic streptococci	36 (23.8)	23 (31.5)	18 (22.2)	
Enterococcus faecalis	41 (27.2)	13 (17.8)	15 (18.5)	
Staphylococcus aureus	24 (15.9)	15 (20.6)	21 (25.9)	
CoNS	10 (6.6)	4 (5.5)	-	
Non-hemolytic streptococci	12 (8.0)	5 (6.9)	5 (6.2)	
Blood culture negative	9 (6.0)	7 (9.6)	9 (11.1)	
Other	19 (12.6)	6 (8.2)	13 (16.0)	

IE: infective endocarditis, IQR: interquartile range, CoNS: Coagulase negative staphylococci, mm: milimeter.
**Defined as at least two drugs of antihypertensive medication (see Supplementary Table 1)

Highlight

- We linked the East Danish Endocarditis Registry with nationwide registries.
- A total of 305 patients surviving infective endocarditis were included.
- Residual vegetation was assessed with echocardiography at discharge.
- Patients with >5 mm vegetation were associated with increased risk of stroke.
- No difference in the associated risk of recurrence of IE or mortality was seen.

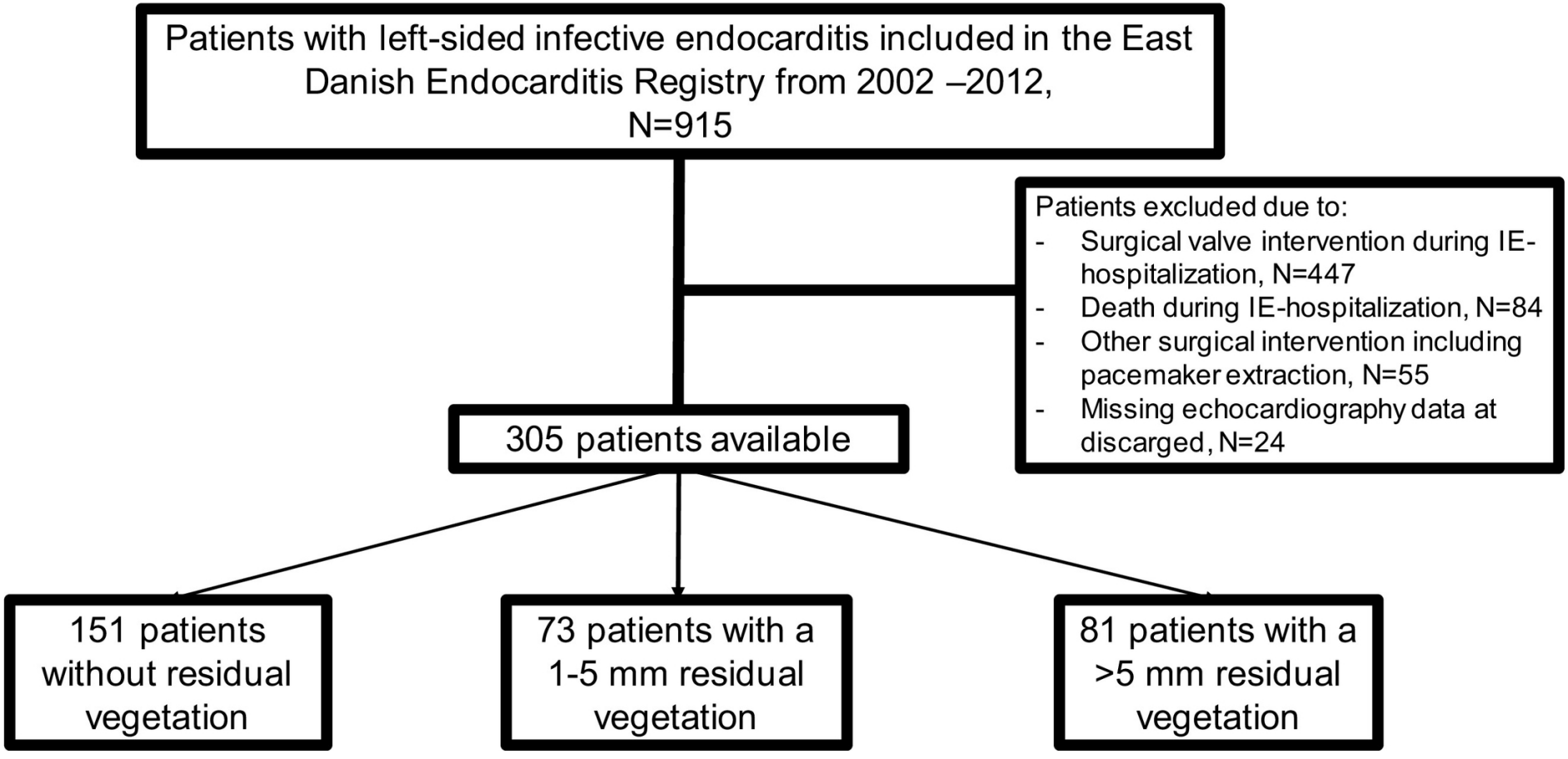
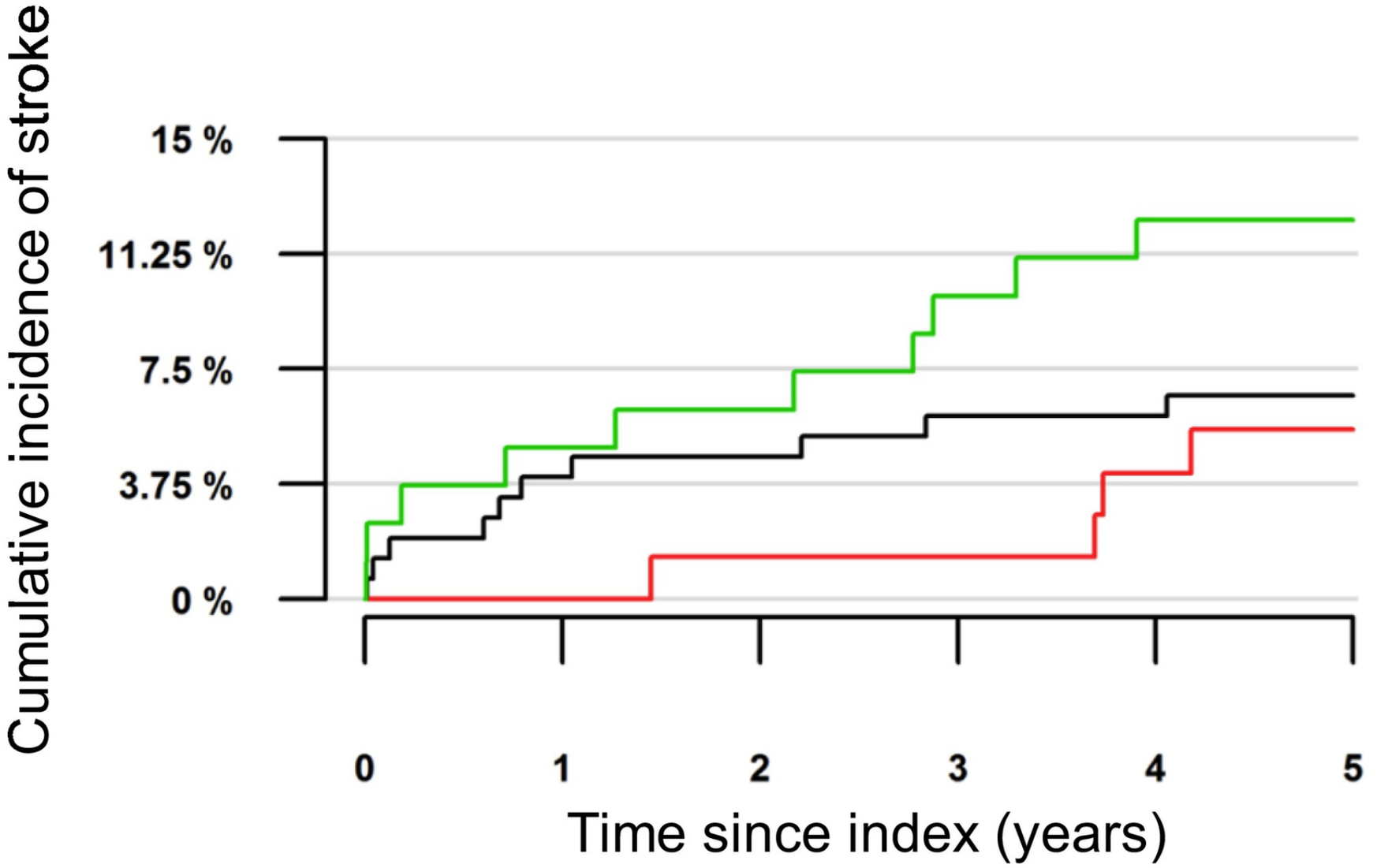

Patients with left-sided infective endocarditis included in the East Danish Endocarditis Registry from 2002 –2012, N=915
Patients excluded due to:
- Surgical valve intervention during IE-hospitalization, N=447
- Death during IE-hospitalization, N=84
- Other surgical intervention including pacemaker extraction, N=55
- Missing echocardiography data at discarged, N=24
305 patients available
151 patients without residual vegetation
73 patients with a 1-5 mm residual vegetation
81 patients with a >5 mm residual vegetation

Figure 1



Patients at risk						
No vegetation	151	113	98	89	83	44
1-5 mm vegetation	73	55	46	39	31	15
>5 mm vegetation	81	49	41	34	32	23

Figure 2

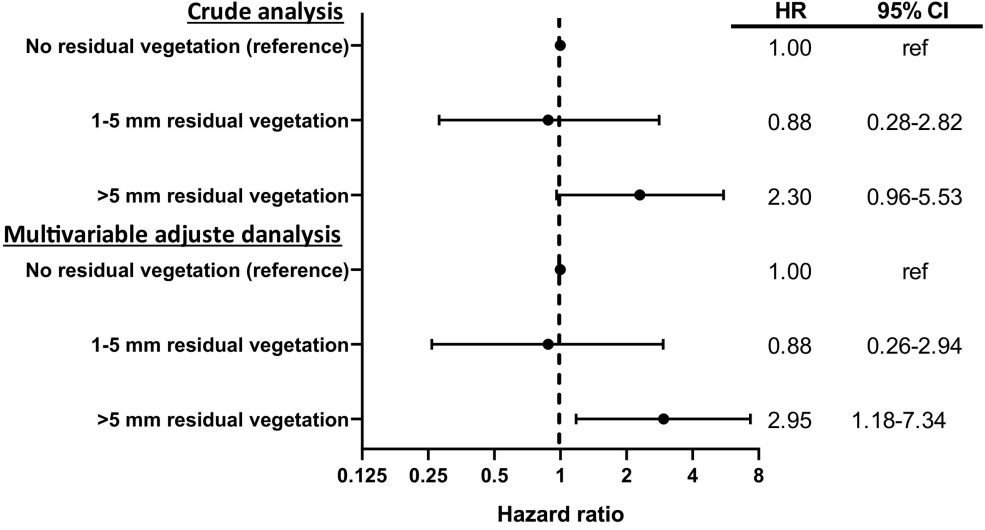

Crude analysis
HR
95% CI
No residual vegetation (reference)
1.00
ref
1-5 mm residual vegetation
0.88
0.28-2.82
>5 mm residual vegetation
2.30
0.96-5.53
Multivariable adjuste danalysis
No residual vegetation (reference)
1.00
ref
1-5 mm residual vegetation
0.88
0.26-2.94
>5 mm residual vegetation
2.95
1.18-7.34
0.125
0.25
0.5
1
2
4
8
Hazard ratio

Figure 3